CH-7913
LeA 36,338

CHIRAL MONOPHOSPHORUS COMPOUNDS AND THEIR TRANSITION METAL COMPLEXES

BACKGROUND OF THE INVENTION

Field of the Invention: The present invention relates to chiral monophosphorus compounds and their transition metal complexes, to a process for preparing chiral monophosphorus compounds and their transition metal complexes and also to their use in asymmetric syntheses.

Brief Description of the Prior Art: Enantiomerically enriched chiral compounds are valuable starting substances for preparing agrochemicals and pharmaceuticals. Asymmetric catalysis has gained great industrial significance for the synthesis of such enantiomerically enriched chiral compounds.

Recent publications in the field of asymmetric synthesis show clearly that transition metal complexes of monophosphorus compounds are very suitable as catalysts in reactions conducted asymmetrically, in particular in asymmetric hydrogenations of C=O, C=N and C=C bonds. For example, A. Alexakis, Tetrahedron Asymmetry, 1997, 8, 3193-3196; W. Chen, J. Xiao, Tetrahedron Letters, 42, 2001, 2897-2899; M. Reetz, G. Mehler, Angew. Chem., 2000, 112, 4047-4049 and WO-A 01/94278 disclose the use of optically active monophosphites or their transition metal complexes for asymmetric hydrogenations.

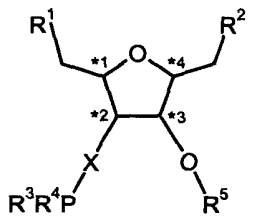
The use of optically active monophosphoramidites or their transition metal complexes in asymmetric syntheses is disclosed, for example, by M. van den Berg et al., J. Am. Chem. Soc., 2000, 122, 11539-11540, WO-A 02/04466; H. Waldmann, Chem. Eur. J. 2000, 6, 671-675; the use of chiral monophosphonites, for example, by C. Claver et al., Chem. Commun., 2000, 961-962.

A disadvantage of the cited monophosphorus compounds is that steric and electronic variation of the ligand framework which is necessary for optimization and adaptation of the ligands and therefore the catalyst for a given substrate is possible only to a very limited extent, and only by numerous, complicated synthetic steps. This disadvantage distinctly limits industrial utilization of such ligands and the catalysts preparable therefrom.

There was therefore the need to develop a ligand system whose steric and electronic properties can be easily varied and which is based on monophosphorus compounds, and whose transition metal complexes, as catalysts in asymmetric synthesis, in particular asymmetric hydrogenations, enable high enantioselectivities.

SUMMARY OF THE INVENTION

Compounds have now been found of the formula (I)



(I)

where

*1, *2, *3 and *4 are each independently a stereogenic carbon atom which has R- or S- configuration,

X is absent or is oxygen and

R^1 and R^2 may each independently be hydrogen, C_1-C_{20}-alkyl, C_1-C_{20}-fluoroalkyl, C_2-C_{20}-alkenyl, C_4-C_{24}-aryl, C_5-C_{25}-arylalkyl, C_6-C_{26}-

arylalkenyl or NR^6R^7, OR^7, -(C_1-C_8-alkyl)-OR^7, -(C_1-C_8-alkyl)-NR^6R^7 or -O_2CR^7,

where R^6 and R^7 are each independently C_1-C_8-alkyl, C_5-C_{15}-arylalkyl or C_4-C_{14}-aryl, or R^6 and R^7 together are a cyclic amino radical having a total of 4 to 20 carbon atoms,

or R^1 and R^2 are each independently radicals of the formula (IIa)

$$-R^8\text{-}SiR^9R^{10}R^{11} \qquad \text{(IIa)}$$

where

R^8 is absent or is oxygen or methylene and

R^9, R^{10} and R^{11} are each independently C_1-C_{12}-alkyl, C_5-C_{15}-arylalkyl or C_4-C_{14}-aryl and

R^3 and R^4 are each independently R^{12}, OR^{13} or $NR^{14}R^{15}$ where R^{12}, R^{13}, R^{14} and R^{15} are each independently C_1-C_{12}-alkyl, C_5-C_{15}-arylalkyl or C_4-C_{14}-aryl, or $NR^{14}R^{15}$ together is a cyclic amino radical having 4 to 20 carbon atoms, or R^3 and R^4 together are -O-R^{16}-O- where R^{16} is a radical selected from the group of C_2-C_4-alkylene, 1,2-phenylene, 1,3-phenylene, 1,2-cyclohexylene, 1,1′-ferrocenylene, 1,2-ferrocenylene, 2,2'-(1,1'-binaphthylene), 2,2′-(1,1′)-biphenylene and 1,1′-(diphenyl-2,2′-methylene) diyl, and the radicals mentioned may optionally be mono- or polysubstituted by radicals selected from the group of fluorine, chlorine, C_1-C_8-alkoxy and C_1-C_8-alkyl and

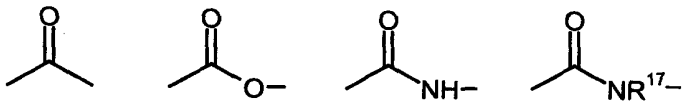
R^5 is hydrogen, C_1-C_{20}-alkyl, C_4-C_{24}-aryl, C_5-C_{25}-arylalkyl, C_1-C_{20}-haloalkyl or a radical of the formula (IIb)

A-B-D (IIb)

where

A is absent or is C_1-C_{12}-alkylene

B is a functionality which is selected from the group of



where

R^{17} may be C_1-C_{20}-alkyl, C_4-C_{24}-aryl, C_5-C_{25}-arylalkyl

and

D is C_1-C_8-alkyl, C_4-C_{24}-aryl or C_5-C_{25}-arylalkyl or

B and D, in the case that A is not absent, may together be cyano or $[(C_1$-C_8-alkylene)-$O]_n$-(C_1-C_8-alkyl) where n is an integer between 1 and 8 or

R^{17} and D together are a cyclic amino radical having 4 to 12 carbon atoms.

For the purposes of the invention, all of the general or preferred radical definitions, parameters and illustrations above and cited hereinbelow, i.e. the particular areas and areas of preference also, may be combined as desired.

DETAILED DESCRIPTION OF THE INVENTION

Alkyl, alkylene, alkoxy and alkenyl are each independently a straight-chain, cyclic, branched or unbranched alkyl, alkylene, alkoxy and alkenyl radical respectively, and each of the radicals mentioned may optionally also be substituted by C_1-C_4-alkoxy radicals.

The same applies to the nonaromatic moiety of an aralkyl radical.

C_1-C_4-alkyl is, for example, methyl, ethyl, 2-methoxyethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl, C_1-C_8-alkyl is additionally, for example, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 1-ethylpropyl, cyclohexyl, cyclopentyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-2-methylpropyl, n-heptyl and n-octyl, C_1-C_{12}-alkyl is further additionally, for example, adamantyl, the isomeric menthyls, n-nonyl, n-decyl and n-dodecyl, and C_1-C_{20}-alkyl is still further additionally, for example, n- hexadecyl and n-octadecyl.

C_1-C_8-alkoxy is, for example, methoxy, ethoxy, 2-methoxyethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy and tert-butoxy, n-pentoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, neopentoxy, 1-ethylpropoxy, cyclohexoxy, cyclopentoxy, n-hexoxy and n-octoxy, and C_1-C_{12}-alkoxy is further additionally, for example, adamantoxy, the isomeric menthoxy radicals, n-decoxy and n-dodecoxy.

C_2-C_{20}-alkenyl is, for example, vinyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 2-methyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-1-butenyl, 1-hexenyl, 1-heptenyl, 1-octenyl or 2-octenyl.

Haloalkyl is in each case independently a straight-chain, cyclic, branched or unbranched alkyl radical which is singly, multiply, or fully substituted by chlorine or fluorine atoms.

C_1-C_{20}-haloalkyl is, for example, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, nonafluorobutyl, perfluorooctyl, perfluorododecyl and perfluorohexadecyl.

Aryl is in each case independently a heteroaromatic radical having 5 to 18 framework carbon atoms of which no, one, two or three framework atoms per cycle, but at least one framework carbon atom in the entire molecule, may be substituted by heteroatoms selected from the group of nitrogen, sulphur or oxygen, but is preferably a carbocyclic aromatic radical having 6 to 18 framework carbon atoms.

Examples of carbocyclic aromatic radicals having 6 to 18 framework carbon atoms are phenyl, naphthyl, phenanthrenyl, anthracenyl or fluorenyl, and heteroaromatic radicals having 5 to 18 framework carbon atoms on which no, one, two or three framework carbon atoms per cycle, but at least one framework carbon atom in the entire molecule, may be substituted by heteroatoms selected from the group of nitrogen, sulphur or oxygen are, for example, pyridinyl, oxazolyl, benzofuranyl, dibenzofuranyl or quinolinyl.

The carbocyclic aromatic radical or heteroaromatic radical may also be substituted by up to five identical or different substituents per cycle which are selected from the group of chlorine, fluorine, C_1-C_{12}-alkyl, C_1-C_{12}-haloalkyl, C_1-C_{12}-alkoxy,

di(C_1-C_8-alkyl)amino, COO(C_1-C_8-alkyl), CON(C_1-C_8-alkyl)$_2$, COO(C_1-C_8-arylalkyl), COO(C_4-C_{14}-aryl), CO(C_1-C_8-alkyl), C_5-C_{15}-arylalkyl or tri(C_1-C_6-alkyl)siloxyl.

The same applies to **Aryloxy** radicals.

Arylalkyl is in each case independently a straight-chain, cyclic or branched or unbranched alkyl radical which may be singly, multiply or fully substituted by aryl radicals as defined above.

C_5-C_{25}-Arylalkyl is, for example, benzyl, diphenylbenzyl, triphenylbenzyl (trityl), 1-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 1-phenyl-1-methylethyl, 1-, 2-, 3- or 4-phenylbutyl, 1-phenyl-1-methylpropyl, 1-phenyl-2-methylpropyl, phenyl-1,1-dimethylethyl, 1-, 2-, 3-, 4- or 5-phenylpentyl, phenyl-1-methylbutyl, phenyl-2-methylbutyl, phenyl-3-methylbutyl, phenyl-2,2-dimethylpropyl, phenyl-1-ethylpropyl, 1-naphthylmethyl, 1-naphthylethyl, naphthyl-1-methylethyl, naphthylbutyl, naphthyl-1-methylpropyl, naphthyl-2-methylpropyl, naphthyl-1,1-dimethylethyl, naphthylpentyl, naphthyl-1-methylbutyl, naphthyl-2-methylbutyl, naphthyl-3-methylbutyl, naphthyl-2,2-dimethylpropyl or naphthyl-1-ethylpropyl, and also their isomeric or stereoisomeric forms.

Arylalkenyl is in each case independently a straight-chain, cyclic, branched or unbranched alkenyl radical which may be singly, multiply or fully substituted by aryl radicals as defined above.

C_6-C_{26}-Arylalkenyl is, for example, 1-phenylvinyl or 2-phenylvinyl.

The preferred substitution patterns for compounds of the formula (I) are defined hereinbelow:

*1,*2,*3,*4 together define the following stereoisomers of the central substituted furan ring:

(1R,2R,3R,4R), (1R,2R,3R,4S), (1R,2R,3S,4S), (1R,2S,3S,4S), (1R,2S,3R,4S), (1R,2S,3S,4R), (1R,2R,3S,4R), (1S,2S,3R,4S), (1S,2S,3S,4S), (1S,2S,3S,4R), (1S,2S,3R,4R), (1S,2R,3R,4R), (1S,2R,3S,4R), (1S,2R,3R,4S), (1S,2S,3R,4S), (1R,2R,3S,4R), preferably (1R,2R,3R,4R), (1R,2R,3R,4S), (1R,2S,3S,4S), (1R,2S,3S,4R), (1R,2R,3S,4R), (1S,2S,3R,4S), (1S,2S,3S,4S), (1S,2S,3S,4R), (1S,2R,3R,4R), (1S,2R,3R,4S), (1S,2S,3R,4S), (1R,2R,3S,4R).

R^1 and R^2 are preferably each independently hydrogen, C_1-C_4-alkyl, C_4-C_{14}-aryl, O-R^7, O_2C-R^7, where R^7 is preferably C_1-C_{12}-alkyl, C_5-C_{25}-arylalkyl or C_4-C_{14}-aryl, or $OSiR^9R^{10}R^{11}$, where R^9, R^{10}, and R^{11} are preferably each independently C_1-C_{12}-alkyl or C_4-C_{14}-aryl.

R^1 and R^2 are particularly preferably each independently hydrogen, tert-butoxy, trityloxy, tert-butyldimethylsilyloxy, tert-butyldiphenylsilyloxy, trimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, neopentoxy or 1-adamantoxy.

For the purposes of the invention, preference is in each case given to those compounds of the formula (I) in which R^1 and R^2 are identical.

R^3 and R^4 are preferably each independently R^{12}, OR^{13} or $NR^{14}R^{15}$ where R^{12}, R^{13}, R^{14} and R^{15} are each independently C_1-C_{12}-alkyl or C_4-C_{14}-aryl, or $NR^{14}R^{15}$ together is a cyclic amino radical having 4 to 12 carbon atoms, for example pyrrolidinyl or piperidinyl or R^3 and R^4 together are -O-R^{16}-O- where R^{16} is ethylene, 1,2-phenylene, 1,3-phenylene, 1,2-cyclohexylene, 1,1′-ferrocenylene, di- or tetra-C_1-C_8-alkyl-substituted 1,1′-(diphenyl-2,2′-methylene)diyl, 1,2-ferrocenylene, 2,2'-(1,1'-binaphthylene) or 2,2′-(1,1′)-

biphenylene, and 2,2'-(1,1'-binaphthylene) or 2,2′-(1,1′)-biphenylene is substituted at least in the 6,6′-position by radicals which are selected from the group of C_1-C_8-alkoxy and C_1-C_8-alkyl, and may also be substituted in the 5,5′-, 4,4′-, 3,3′- or 2,2′-position by radicals which are selected from the group of fluorine, chlorine, C_1-C_8-alkoxy and C_1-C_8-alkyl.

R^3 and R^4 are particularly preferably each independently R^{12}, OR^{13} or $NR^{14}R^{15}$, where R^{12} and R^{13} are each independently methyl, ethyl, n-propyl, isopropyl, tert-butyl, cyclohexyl, phenyl, 2-(C_1-C_8)-alkylphenyl such as o-tolyl, 3-(C_1-C_8)-alkylphenyl such as m-tolyl, 4-(C_1-C_8)-alkylphenyl such as p-tolyl, 2,6-di-(C_1-C_8)-alkylphenyl such as 2,6-dimethylphenyl, 2,4-di-(C_1-C_8)-alkylphenyl such as 2,4-dimethylphenyl, 3,5-di-(C_1-C_8)-alkylphenyl such as 3,5-dimethylphenyl, 3,4,5-tri-(C_1-C_8)-alkylphenyl such as mesityl and isityl, 2-(C_1-C_8)-alkoxyphenyl such as o-anisyl and o-phenetyl, 3-(C_1-C_8)-alkoxyphenyl such as m-anisyl and m-phenetyl, 4-(C_1-C_8)-alkoxyphenyl such as p-anisyl and p-phenetyl, 2,4-di-(C_1-C_8)-alkoxyphenyl such as 2,4-dimethoxyphenyl, 2,6-Di-(C_1-C_8)-alkoxyphenyl such as 2,6-dimethoxyphenyl, 3,5-di-(C_1-C_8)-alkoxyphenyl such as 3,5-dimethoxyphenyl, 3,4,5-tri-(C_1-C_8)-alkoxyphenyl such as 3,4,5-trimethoxyphenyl, 3,5-dialkyl-4-(C_1-C_8)-alkoxyphenyl such as 3,5-dimethyl-4-anisyl, 3,5-(C_1-C_8)-dialkyl-4-di-(C_1-C_8)-alkylaminophenyl, 3,5-dimethyl-4-dimethylaminophenyl, 4-di-(C_1-C_8)-alkylaminophenyl such as 4-diethylaminophenyl and 4-dimethylaminophenyl, 3,5-bis-[(C_1-C_4)-fluoroalkyl]phenyl such as 3,5-bis-trifluoromethylphenyl, 2,4-bis-[(C_1-C_4)-fluoroalkyl]phenyl such as 2,4-bis-trifluoromethylphenyl, 4-[(C_1-C_4)-fluoroalkyl]phenyl such as 4-trifluoromethylphenyl and mono-, di-, tri-, tetra- or pentafluorine- and/or –chlorine-substituted phenyl, fluorenyl or naphthyl, such as 4-fluorophenyl and 4-chlorophenyl, and $NR^{14}R^{15}$ as a whole is dimethylamino, diethylamino, pyrrolidino or diisopropylamino. Particular preference is further given to R^3 and R^4 as a pair being O-R^{16}-O,

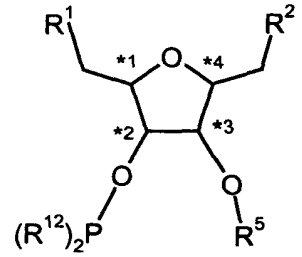
where R^{16} is 1,1′-bis-(4,6-di-(C_1-C_8-alkyl)phenyl)-2,2′-methylene)diyl, in particular 1,1′-bis-(4-methyl-6-tert-butylphenyl-2,2′-methylene)diyl and 1,1′-bis-(4-methyl-6-(1-methylcyclohexyl)phenyl-2,2′-methylene)diyl, or where R^{16} is (R)-1,1'-biphenyl-2,2'-diyl, (S)-1,1'-biphenyl-2,2'-diyl, (R)-1,1'-binaphthyl-2,2'-diyl, (S)-1,1'-binaphthyl-2,2'-diyl, 1,1′-[bis-(4-methyl-6-tert-butylphenyl)-2,2′-methylene)]diyl or 1,1′-[bis-(4-methyl-6-(1-methylcyclohexyl)-2,2′-methylene)]diyl.

R^3 and R^4 are very particularly preferably identical and are each 2,4-dimethylphenyl.

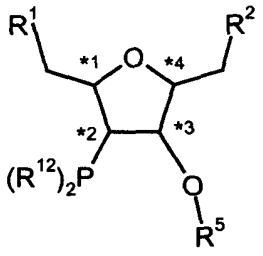
R^5 is preferably hydrogen, C_1-C_4-alkyl, -CO(C_1-C_4-alkyl), benzyl-CO-phenyl or phenyl, and benzyl or phenyl may optionally be further substituted by one, two or three substituents selected from the group of C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkyl.

R^5 is particularly preferably hydrogen, methyl or ethyl.

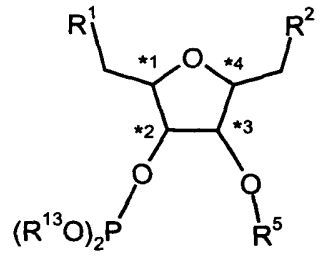
Particularly preferred compounds of the formula (I) are those of the formulae (Ia) to (Id)



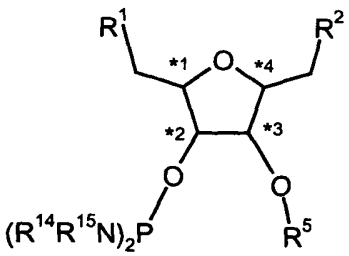
(Ia)



(Ib)



(Ic)



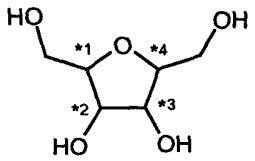
(Id)

where *1,*2,*3,*4, R^1, R^2, R^5, R^{12}, R^{13}, R^{14} and R^{15} are as defined under formula (I).

A particularly preferred compound of the formula (I) is 2-*O*-(di(2,4-dimethyl-phenyl)phosphino)-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol.

For the purposes of the invention, the term stereoisomerically enriched includes stereoisomerically pure compounds or else mixtures of stereoisomeric compounds in which one stereoisomer is present in a greater relative proportion than the other stereoisomer(s), preferably in a relative proportion of 50 to 100 mol%, more preferably 90 to 100 mol% and most preferably 98 to 100 mol%, and includes in particular enantiomerically enriched compounds for which the same definitions apply.

The compounds of the formula (I) or (Ia) to (Id) can be prepared starting from the known 2,5-anhydrocyclopentoses of the formula (III).



(III)

2,5-Anhydrocyclopentoses of the formula (III) are, for example:

2,5-anhydro-D-mannitol, 2,5-anhydro-L-mannitol, 2,5-anhydro-L-iditol, 2,5-anhydro-D-iditol, 2,5-anhydro-L-glucitol, 2,5-anhydro-D-glucitol, 2,5-anhydroaltritol, 2,5-anhydro-D-altritol, 2,5-anhydrogalactitol, 2,5-anhydroallitol.

Preferred compounds of the general formula (III) are:
2,5-anhydro-D-mannitol and 2,5-anhydro-L-iditol.

For the purposes of the invention, preference is given in particular to those compounds of the formula (I) which are obtainable starting from 2,5-anhydro-D-mannitol and 2,5-anhydro-L-iditol by the methods described hereinbelow.

The compounds of the formula (III) can be converted by reacting with compounds of the formula (IV)

$$R^{18}\text{-Hal} \qquad (IV)$$

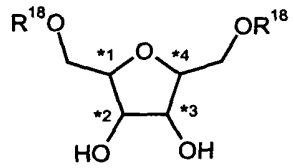
where R^{18} is R^7, R^7CO or $OSiR^9R^{10}R^{11}$ and where R^7, R^9, R^{10} and R^{11} each have the definition and areas of preference specified under formula (I) or R^{18} is R^{19}-SO_2- where

R^{19} is C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, C_5-C_{25}-arylalkyl or C_4-C_{24}-aryl

and

Hal is chlorine, bromine or iodine

to compounds of the formula (V)



(V)

where

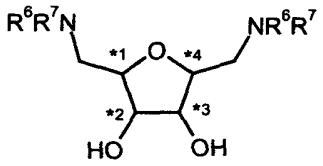
R^{18} is in each case independently as defined under formula (IV).

Compounds of the formula (V) in which R^{18} is $R^{19}SO_2$- can also be converted by reacting with amines of the formula (VI)

$$HNR^6R^7 \qquad (VI)$$

where

R^7 and R^8 each independently have the definitions and areas of preference specified under formula (I) to compounds of the formula (VII)



(VII)

where

R^6 and R^7 are each independently as defined under formula (IV).

Compounds of formula (V) in which R^{18} is $R^{19}SO_2$- can also be converted by reacting with complex hydrides of the formula (VIII)

$$Met^1(AlR^{20}{}_nR^{21}{}_{(4-n)}) \qquad (VIII)$$

where

Met^1 is lithium, sodium or potassium, preferably lithium,

R^{20} is hydrogen

n is 1, 2, 3 or 4, preferably 4 and

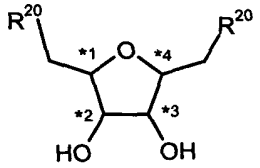
R^{21} is C_1-C_4-alkyl

or by reacting with organolithium compounds of the formula (IX)

$$R^{20}\text{-Li} \qquad \text{(IX)}$$

where

R^{20} is C_1-C_{20}-alkyl, C_1-C_{20}-fluoroalkyl, C_2-C_{20}-alkenyl, C_4-C_{24}-aryl, C_5-C_{25}-arylalkyl, C_6-C_{26}-arylalkenyl, -(C_1-C_8-alkyl)-OR^8, -(C_1-C_8-alkyl)-NR^7R^8 or protected (for example as a cyclic acetal) -(C_1-C_8-alkyl)-CO-R^8 to compounds of the formula (X)



(X)

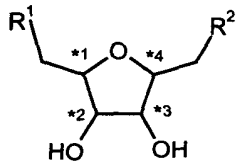
where

R^{20} is as defined under formulae (VIII) and (IX).

As a consequence of the acidity of the free 2- and 3-hydroxyl groups, it is advantageous to use an excess of the organolithium compounds or of the complex hydrides, or to protect the 3,4-diol unit in a manner known per se by conversion, for example, to a cyclic acetal and subsequent deprotection.

The compounds of the formulae (V), (VII) and (X) together are encompassed by the compounds of the formula (XI) which can be used as intermediates in preparing the compounds of the formula (I) according to the invention.

In formula (XI)



(XI),

R^1 and R^2 have the same definition and areas of preference as described under formula (I).

The compounds of the formula (XI) can be used in a manner known in principle (see also Rajan Babu, J. Org. Chem., 1997, 62, 6012-6028) by reacting with compounds of the formula (XII)

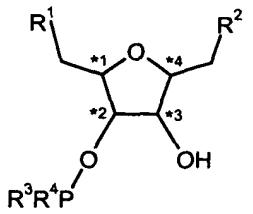
$$R^3R^4P\text{-}Y \qquad (XII)$$

where

R^3 and R^4 have the same definition and areas of preference as specified under formula (I) and

Y is chlorine, bromine, iodine, dimethylamino or diethylamino, preferably chlorine,

to obtain the compounds of the formula (Ie)



(Ie)

where

R^1, R^2, R^3 and R^4 each have the same definition and areas of preference as described under formula (I).

The compounds of the formula (Ie) can also be reacted with compounds of the formula (XIII)

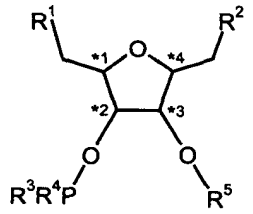
$$R^5Z \quad (XIII)$$

where

R^5 has the same definitions and areas of preference as specified under formula (I) and

Z is chlorine, bromine, iodine or $R^{19}SO_3$ and, in the case that R^5 is to be bonded via a carbonyl group, may also be R^5O-

to give compounds of the formula (If),



(If)

where

R^1, R^2, R^3, R^4, and R^6 each have the same definitions and areas of preference as specified under formula (I) and R^5 is not hydrogen.

Advantageously, the conversion to compounds of the formula (Ie) or (If) is effected after at least partial deprotonation of the alcohol function or in the presence of a base which can at least partially deprotonate the alcohol function.

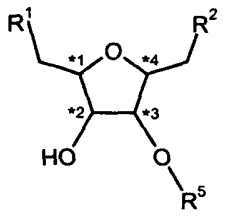
Preferred bases for the conversion to compounds of the formula (Ie) are amines or N-heteroaromatics, in particular pyridine, and for the conversion to compounds of the formula (If), carbonates, hydroxides, alkoxides, amides and hydrides of alkali metals or alkaline earth metals, or amines or N-heteroaromatics, in particular pyridine.

Examples of suitable solvents for the conversion to compounds of the formula (Ie) are chlorinated alkanes such as methylene chloride, aliphatic hydrocarbons, e.g. hexane, cyclohexane, optionally chlorinated aromatic hydrocarbons, e.g. chlorobenzene, toluene, pyridine, benzene, ketones, e.g. acetone, or carboxylic esters, e.g. ethyl acetate, or dialkyl ethers, e.g. THF or methyl tert-butyl ether. The solvent used is preferably methylene chloride.

Suitable solvents for the conversion to compounds of the formula (If) are in principle the same solvents as for the conversion to compounds of the formula (Ie), although when strong bases such as hydroxides, alkoxides, amides and hydrides are used, it is advantageous to use no chlorinated alkanes.

The invention in particular also encompasses the compounds of the formula (If). The same definitions and areas of preference specified under formula (I) apply.

However, in a preferred embodiment, the compounds of the formula (If) are prepared by initially reacting compounds of the formula (Ie) with compounds of the formula (XIII) to give compounds of the formula (XIV)



(XIV)

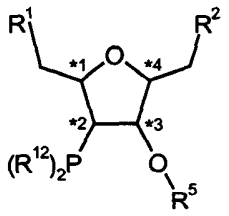
where

R^1, R^2, R^3, R^4, and R^6 each have the same definitions and areas of preference as specified under formula (I) and R^5 is not hydrogen, and then reacting the compounds of the formula (XIV) with compounds of the formula (XII) to give compounds of the formula (If).

The same information on solvents and bases applies as for the process via the compounds of the formula (Ie).

The compounds of the formula (XIV) are likewise encompassed by the invention.

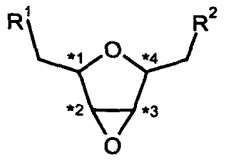
Compounds of the formula (Ib)



(Ib)

where

R^1, R^2, R^5, R^6 and R^{12} each have the definitions and areas of preference specified under formula (I) can also be prepared by a process according to the invention by converting compounds of the formula (XV)



(XV)

where

R^1 and R^2 have the definition and areas of preference specified under formula (I), in the presence of compounds of the formula (XVI),

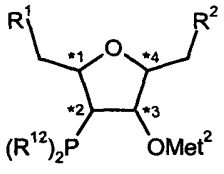
$$(R^{12})_2PMet^2 \quad (XVI)$$

where

Met^2 is lithium, sodium or potassium and

R^{12} has the definition and areas of preference specified under formula (I)

to compounds of the formula (XVII),



(XVII)

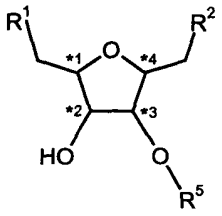
where

R^1, R^2, Met^2 and R^{12} are each as defined above

and reacting the compounds of the formula (XVII) with compounds of the formula (XIII) as defined there to give compounds of the formula (Ib).

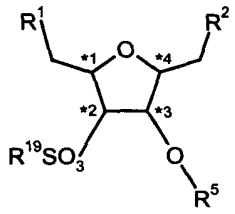
Alternatively, the compounds of the formula (XVII) can be converted by acidifying to compounds of the formula (Ib) in which R^5 is hydrogen.

The compounds of the formula (Ib) can also be prepared, for example, by initially converting the compounds of the formula (XIV)



(XIV)

as defined above in a manner known per se (see also Terfort, Synthesis, 1992, 951-953) to compounds of the formula (XVIII)



(XVIII)

where

R^1 and R^2 each have the definition and areas of preference specified under formula (I) and R^{19} has the definition and areas of preference specified under formula (IV), and then reacting the compounds of the formula (XVIII) with phosphides of the formula (XVI).

The compounds of the formula (XVIII) are likewise encompassed by the invention.

The invention further encompasses transition metal complexes which contain the compounds of the formula (I) according to the invention.

Transition metal complexes are preferably those of ruthenium, osmium, cobalt, rhodium, iridium, nickel, palladium, platinum and copper, preferably those of ruthenium, rhodium, iridium, nickel, palladium, platinum and copper.

The transition metal complexes according to the invention are suitable in particular as catalysts. The invention therefore also encompasses catalysts which contain the transition metal complexes according to the invention.

The catalysts used may, for example, either be isolated transition metal complexes or those transition metal complexes which are obtainable by reacting transition metal compounds and compounds of the formula (I).

Isolated transition metal complexes which contain the compounds of the formula (I) are preferably those in which the ratio of transition metal to compound of the formula (I) is 1:2, 1:3 or 1:4.

Preference is given to the compounds according to the invention of the formula (XIX)

$$[(I)_4M] \qquad (XIX)$$

where

(I) is a compound of the formula (I) with the definition and the areas of preference specified there and

M is rhodium or iridium.

Preferred transition metal complexes are those which are obtainable by reacting transition metal compounds and compounds of the formula (I).

Suitable transition metal compounds are, for example, those of the formula (XXa)

$$M(An^1)_q \qquad (XXa)$$

where

M is rhodium, iridium, ruthenium, nickel, palladium, platinum or copper and

An^1 is chloride, bromide, acetate, nitrate, methanesulphonate, trifluoromethanesulphonate or acetylacetonate and

q is 3 for rhodium, iridium and ruthenium, is 2 for nickel, palladium and platinum, and is 1 for copper,

or transition metal compounds of the formula (XXb)

$$M(An^2)_qL^1{}_2 \qquad (XXb)$$

where

M is ruthenium, iridium, ruthenium, nickel, palladium, platinum or copper and

An^2 is chloride, bromide, acetate, methanesulphonate or trifluoromethanesulphonate, tetrafluoroborate or hexafluorophosphate, perchlorate, hexafluoroantimonate, tetra(bis-3,5-trifluoromethylphenyl)-borate or tetraphenylborate and

q is 1 for rhodium and iridium, is 2 for ruthenium, nickel, palladium and platinum, and is 1 for copper,

L^1 is in each case C_2-C_{12}-alkene, for example ethylene or cyclooctene, or a nitrile, for example acetonitrile, benzonitrile or benzyl nitrile, or

$L^1{}_2$ together is a (C_4-C_{12})-diene, for example bicyclo[2.1.1]hepta-2,5-diene (norbornadiene) or 1,5-cyclooctadiene,

or transition metal compounds of the formula (XXc)

$$[ML^2An^1{}_2]_2 \qquad \text{(XXc)}$$

where

M is ruthenium and

L^2 is an aryl radical, for example cymene, mesityl, phenyl or cyclooctadiene, norbornadiene or methylallyl,

or transition metal compounds of the formula (XXd)

$$Met^3{}_q[M(An^3)_4] \qquad \text{(XXd)}$$

where

M is palladium, nickel, iridium or rhodium and

An^3 is chloride or bromide and

Met^3 is lithium, sodium, potassium, ammonium or an organic ammonium ion and

q is 3 for rhodium and iridium, and is 2 for nickel, palladium and platinum,

or transition metal compounds of the formula (XXe)

$$[M(L^3)_2]An^4 \qquad (XXe)$$

where

M is iridium or rhodium and

L^3 is (C_4-C_{12})-diene, for example bicyclo[2.1.1]hepta-2,5-diene (norbornadiene) or 1,5-cyclooctadiene and

An^4 is a noncoordinating or weakly coordinating anion, for example methanesulphonate, trifluoromethanesulphonate, tetrafluoroborate, hexafluorophosphate, perchlorate, hexafluoroantimonate, tetra(bis-3,5-trifluoromethylphenyl)borate or tetraphenylborate.

Suitable transition metal compounds are additionally, for example, Ni(1,5-cyclooctadiene)$_2$, Pd_2(dibenzylideneacetone)$_3$, Pd[PPh_3]$_4$, cyclopentadienyl$_2$Ru, Rh(acac)(CO)$_2$, Ir(pyridine)2(1,5-cyclooctadiene), Cu(phenyl)Br, Cu(phenyl)Cl, Cu(phenyl)I, Cu(PPh_3)$_2$Br, [Cu(CH_3CN)$_4$]BF_4 and [Cu(CH_3CN)$_4$]PF_6 or multinuclear bridged complexes, for example [Rh(1,5-cyclooctadiene)Cl]$_2$, [Rh(1,5-cyclooctadiene)Br]$_2$, [Rh(ethene)$_2$Cl]$_2$, and [Rh(cyclooctene)$_2$Cl]$_2$.

The transition metal compounds used are preferably:
[Rh(cod)Cl]$_2$, [Rh(cod)Br]$_2$, [Rh(cod)$_2$]ClO_4, [Rh(cod)$_2$]BF_4, [Rh(cod)$_2$]PF_4, [Rh(cod)$_2$]ClO_6, [Rh(cod)$_2$]OTf, [Rh(cod)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), [Rh(cod)$_2$]SbF_6, $RuCl_2$(cod), [(cymene)$RuCl_2$]$_2$, [(benzene)$RuCl_2$]$_2$, [(mesityl)$RuCl_2$]$_2$, [(cymene)$RuBr_2$]$_2$, [(cymene)RuI_2]$_2$, [(cymene)Ru(BF_4)$_2$]$_2$, [(cymene)Ru(PF_6)$_2$]$_2$, [(cymene)Ru(BAr_4)$_2$]$_2$ (Ar = 3,5-

bistrifluoromethylphenyl), [(cymene)Ru(SbF_6)$_2$]$_2$, [Ir(cod)Cl]$_2$, [Ir(cod)$_2$]PF_6, [Ir(cod)$_2$]ClO_4, [Ir(cod)$_2$]SbF_6, [Ir(cod)$_2$]BF_4, [Ir(cod)$_2$]OTf, [Ir(cod)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), $RuCl_3$, $NiCl_3$, $RhCl_3$, $PdCl_2$, $PdBr_2$, Pd(OAc)$_2$, Pd_2(dibenzylideneacetone)$_3$, Pd(acetylacetonate)$_2$, CuOTf, CuI, CuCl, Cu(OTf)$_2$, CuBr, CuI, $CuBr_2$, $CuCl_2$, CuI_2, [Rh(nbd)Cl]$_2$, [Rh(nbd)Br]$_2$, [Rh(nbd)$_2$]ClO_4, [Rh(nbd)$_2$]BF_4, [Rh(nbd)$_2$]PF_6, [Rh(nbd)$_2$]OTf, [Rh(nbd)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), [Rh(nbd)$_2$]SbF_6, $RuCl_2$(nbd), [Ir(nbd)$_2$]PF_6, [Ir(nbd)$_2$]ClO_4, [Ir(nbd)$_2$]SbF_6, [Ir(nbd)$_2$]BF_4, [Ir(nbd)$_2$]OTf, [Ir(nbd)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), Ir(pyridine)$_2$(nbd), [Ru(DMSO)$_4$$Cl_2$], [Ru($CH_3CN$)$_4$$Cl_2$], [Ru(PhCN)$_4$$Cl_2$], [Ru(cod)$Cl_2$]$_n$, [Ru(cod)$_4$(methallyl)$_2$], [Ru(acetylacetonate)$_3$].

Greater preference is given to [Rh(cod)Cl]$_2$, [Rh(cod)Br]$_2$, [Rh(cod)$_2$]ClO_4, [Rh(cod)$_2$]BF_4, [Rh(cod)$_2$]PF_4, [Rh(cod)$_2$]ClO_6, [Rh(cod)$_2$]OTf, [Rh(cod)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), [Rh(cod)$_2$]SbF_6, [Rh(nbd)Cl]$_2$, [Rh(nbd)Br]$_2$, [Rh(nbd)$_2$]ClO_4, [Rh(nbd)$_2$]BF_4, [Rh(nbd)$_2$]PF_6, [Rh(nbd)$_2$]OTf, [Rh(nbd)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl), [Rh(nbd)$_2$]SbF_6, [Ir(cod)Cl]$_2$, [Ir(cod)$_2$]PF_6, [Ir(cod)$_2$]ClO_4, [Ir(cod)$_2$]SbF_6, [Ir(cod)$_2$]BF_4, [Ir(cod)$_2$]OTf, [Ir(cod)$_2$]BAr_4 (Ar = 3,5-bistrifluoromethylphenyl).

The amount of the metal in the transition metal compounds used may, for example, be 5 to 100 mol%, based on the compound of the formula (I) used, preferably 10 to 50 mol% and most preferably 15 to 50 mol%.

The catalysts which contain the transition metal complexes according to the invention are suitable in particular for use in a process for preparing stereoisomerically enriched, preferably enantiomerically enriched, compounds.

Preference is given to using the catalysts for asymmetric 1,4-additions, asymmetric hydroformylations, asymmetric hydrocyanations, asymmetric Heck

reactions and asymmetric hydrogenations, particular preference to using them for asymmetric hydrogenations.

Preferred asymmetric hydrogenations are, for example, hydrogenations of prochiral C=C-bonds, for example prochiral enamines, olefins, enol ethers, C=O bonds, for example prochiral ketones, and C=N bonds, for example prochiral imines. Particularly preferred asymmetric hydrogenations are hydrogenations of prochiral C=C bonds, for example prochiral enamines, olefins and C=N bonds, for example prochiral imines.

The invention therefore also encompasses a process for preparing stereoisomerically enriched, preferably enantiomerically enriched, compounds by catalytic hydrogenations of olefins, enamines, enamides, imines or ketones, which is characterized in that the catalysts used are those which contain transition metal complexes of compounds of the formula (I) as defined there.

The amount of the transition metal compound or of the transition metal complex used may, for example, be 0.001 to 5 mol%, based on the substrate used, preferably 0.001 to 0.5 mol%, very particularly preferably 0.001 to 0.1 mol% and even more preferably 0.001 to 0.008 mol%.

In a preferred embodiment, asymmetric hydrogenations can be carried out, for example, in such a way that the catalyst is formed from a transition metal compound and compound of the formula (I), optionally in a suitable solvent, the substrate is added and the reaction mixture is put under hydrogen pressure at room temperature.

The metal compounds used for asymmetric hydrogenations are particularly preferably those of general formula (XXI)

$$[M(L^3)_2]An^4 \qquad (XXI)$$

where M is rhodium or iridium and L^3 and An are each as defined above,

or dinuclear complexes, for example $[Rh(1,5\text{-cyclooctadiene})Cl]_2$, $[Rh(1,5\text{-cyclooctadiene})Br]_2$, $[Rh(ethene)_2Cl]_2$, $[Rh(cyclooctene)_2Cl]_2$.

Particularly preferred metal compounds for asymmetric hydrogenations are $[Rh(cod)_2]OTf$, $[Rh(cod)_2]BF_4$, $[Rh(cod)_2]PF_6$, $[Rh(nbd)_2]PF_6$, $[Rh(nbd)_2]BF_4$, and $[Rh(norbornadiene)_2]OTf$, $[Ir(cod)_2]BF_4$ and $[Ir(cod)_2PF_6]$.

In a particularly preferred embodiment, transition metal compound and compound of the formula (I) are dissolved in degassed solvent in a baked-out glass autoclave. The mixture is stirred for approx. 5 min and the substrate is subsequently added in degassed solvent. After setting a particular temperature, hydrogenation is effected at elevated H_2 pressure.

Useful solvents for asymmetric catalysis are, for example, chlorinated alkanes such as methyl chloride, short-chain C_1-C_6-alcohols, e.g. methanol, isopropanol or ethanol, aromatic hydrocarbons, e.g. toluene or benzene, ketones, e.g. acetone, or carboxylic esters, e.g. ethyl acetate.

The asymmetric catalysis is advantageously carried out at a temperature of –20°C to 200°C, preferably 0 to 100°C and more preferably at 20° to 70°C.

The hydrogen pressure may, for example, be 0.1 to 200 bar, preferably 0.5 to 100 bar and more preferably 1 to 70 bar.

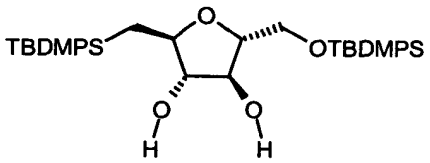
The catalysts according to the invention are suitable in particular in a process for preparing stereoisomerically enriched, preferably enantiomerically enriched, active

ingredients in pharmaceuticals and agrochemicals, or intermediates of these two classes.

The advantage of the present invention is that ligands can be prepared in an efficient manner and their electronic and steric properties can be varied to a wide degree starting from readily available reactants. Furthermore, the ligands according to the invention and their transition metal complexes exhibit high enantioselectivities, especially in asymmetric hydrogenations of C=C bonds and imines.

EXAMPLES

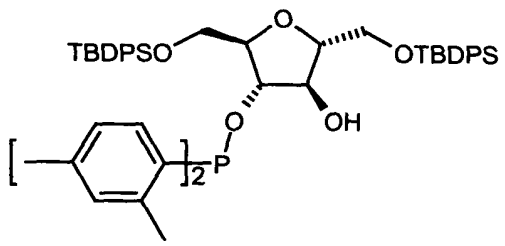
Example 1:



1,6-Di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (B1): 3 ml (11.66 mmol) of *tert*-butyldiphenylsilyl chloride (TBDMPSCl) were added dropwise at 0°C to a solution of 0.87 g (5.3 mmol) of 2,5-anhydro-D-mannitol and 1.5 g (22.28 mmol) of imidazole in 12 ml of anhydrous DMF. The mixture was heated to room temperature and stirred for a further 25 hours, and the solvent was subsequently removed under reduced pressure. The mixture was diluted using CH_2Cl_2 and washed with water, and the organic phase was dried over Na_2SO_4 and the solvent subsequently removed under reduced pressure. The crude product was purified by means of column chromatography (4:1 hexane/ethyl acetate). Yield 1.36 g (40% of theory). ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.81-7.30 (m, 10H, Ph); 4.25 (m, 1H, H-3); 4.17 (m, 1H, H-2); 4.04 (d, 1H, OH); 3.86 (dd, 1H, $J_{6,2}$= 3.7 Hz, $J_{6,6'}$=11.1 Hz, H-6); 3.75 (dd, 1H, $J_{6',2}$= 3.2 Hz, $J_{6,6'}$=11.1 Hz, H-6'); 1.07 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (100.6 MHz) δ, 136.10-126.99 (Ph), 87.09 (C-2), 79.71 (C-3), 65.52 (C-6), 26.73 (C(C$\underline{H}_3$)$_3$), 19.02 ($\underline{C}$(CH$_3$)$_3$).

Example 2:

2-*O*-(Di(2,4-dimethylphenyl)phosphino)-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (B2):



A solution of 169 mg (0.610 mmol) of bis-(2,4-dimethylphenyl)chlorophosphine in 2 ml of anhydrous THF was added to a solution of 300 mg (0.468 mmol) of 1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (**B1**) and 0.26 ml of anhydrous Et_3N (1.86 mmol) and stirred at room temperature overnight. After adding ethyl ether, the mixture was filtered through Celite®, the solvent removed under reduced pressure and the crude product purified by means of column chromatography. Yield 190 mg (49% of theory). ^1H NMR (400 MHz, $CDCl_3$) δ, 7.59-6.87 (m, 26H, arom.), 4.47 (m, 1H, CH), 4.31 (m, 1H, CH), 3.99 (m, 2H, CH), 3.69 (m, 3H, CH_2), 3.54 (dd, 1H, CH_2), 2.79 (s, OH), 2.30 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 0.96 (s, 9H, CH_3), 0.94 (s, 9H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ, 138.1-127.6 (CH, C, arom.), 86.0 ($^2J_{C-P}$=18 Hz, CH), 84.9 (CH), 83.9 ($^3J_{C-P}$=6.13 Hz, CH), 78.0 ($^2J_{C-P}$=4.5 Hz, CH CH), 64.7 (CH_2), 64.1 (CH_2), 27.1 (CH_3), 27.0 (CH_3), 21.4 (C), 20.5 (d, ^3J=48.4 Hz, CH_3), 20.3 (d, ^3J=48.4 Hz, CH_3), 19.6 (s, CH_3), 19.5 (s, CH_3). ^{31}P NMR (161.9 MHz, $CDCl_3$) δ, 102.9.

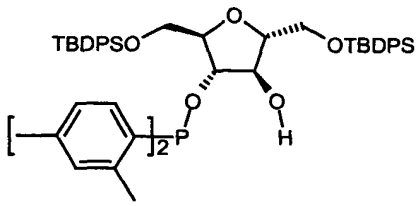
Rhodium-catalysed hydrogenation of enamides

Examples 3 and 4:

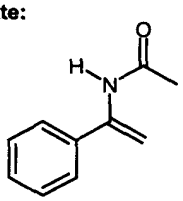
0.01 or 0.005 molar equivalent of transition metal compound and 0.027 molar equivalent of ligand were dissolved under argon in degassed CH_2Cl_2 (0.015 M) and stirred at room temperature for 1/2 hour. After adding one molar equivalent of substrate in degassed CH_2Cl_2 (0.08 M) under argon, the mixture obtained was

hydrogenated in an autoclave at an appropriate temperature under hydrogen pressure. Conversion and ee were determined by chromatography.

Ligand:



Substrate:



The results of the hydrogenations are compiled in Table 1.

Table 1

Example	mol% of ligand	Metal precursor	mol% of metal precursor	T (°C)	P (bar)	Time (h)	Conversion (%)	ee (%)
3	2.7	$[Rh(nbd)_2]PF_6$	1	25	3.5	16	96	18
4	2.7	$[Rh(cod)Cl_2]_2$	0.5	25	30	24	100	83

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.